Remarks

Interfering Subject Matter

The paper mailed December 3, 2004 stated that "[a]t least claim(s) 42 of the application are believed to interfere . . . with at least claim(s) 26 of U.S. Patent 6,593,098." Claim 42 of the present application is directed to an isolated huBUB3 polypeptide. Claim 26 of U.S. Patent 6,593,098 is directed to an isolated nucleic acid molecule encoding a huBUB3 polypeptide. U.S. Patent 6,593,098 also includes claims to huBUB3 protein (claim 28), nucleic acid molecules encoding huBUB3 (claims 21-26), RNA molecules transcribed from the nucleic acid molecules (claim 25), and antibodies that are immunologically specific for huBUB3 (claim 29).

Applicant has added new claims directed to a huBUB3 polypeptide (claim 49), nucleic acid molecules encoding huBUB3 (claims 50-52), RNA molecules transcribed from the nucleic acid molecules (claim 53), and antibodies that are immunologically specific for huBUB3 (claim 54). Each of these new claims is supported in Applicant's specification. The following table compares claim 42 and new claims 49-54 with claims 28, 21-26, and 29 of Yen, U.S. Patent 6,593,098 and provides support for each of new claims 49-54 in the present application and Applicant's priority document, Serial No. 60/070,182. Applicant requests entry of claims 49-54 so that, if an interference is declared, priority to all of the interfering subject matter can be addressed efficiently in a single proceeding.

pending claims[1]	claims of Yen, U.S. Patent 6,593,098
42. (previously presented) An isolated huBUB3 polypeptide comprising amino acids from about 1 to about 328 of SEQ ID NO:2. **49.** (new) An isolated huBUB3 polypeptide comprising amino acids 1-328 of SEQ ID NO:2. *Serial No. 10/084,700: original claim 42; SEQ ID NO:2* *Serial No. 60/070,182: claim 37; Fig. 2 (SEQ ID NO:2)*	**28.** An isolated human BUB3 protein about 348 amino acids in length comprising SEQ ID NO:6, said encoded protein complexing with human BUB1A kinase.
50. (new) An isolated double-stranded nucleic acid molecule which comprises SEQ ID NO:1. *Serial No. 10/084,700: page 14, lines 25-27* *Serial No. 60/070,182: claim 29; Fig. 1 (SEQ ID NO:1)*	**21.** An isolated double-stranded nucleic acid molecule which, upon denaturation, comprises SEQ ID NO: 5, said nucleic acid molecule comprising a sequence encoding a human BUB3 protein about 348 amino acids in length, said BUB3 protein comprising five WD-40 repeat motifs and complexing with human BUB1A kinase. **26.** An isolated nucleic acid molecule comprising a sequence selected from the group consisting of: a) SEQ ID NO:5; and b) a sequence encoding a polypeptide of SEQ ID NO:6.
51. (new) The nucleic acid molecule of claim 50 which is DNA. *Serial No. 10/084,700: page 17, lines 9-12* *Serial No. 60/070,182: page 14, par. 1*	**22.** The nucleic acid molecule of claim 21, which is DNA.

[1] The present application, Serial No. 10/084,700, claims the benefit of Serial No. 60/070,182 filed December 30, 1997.

52. (new) The nucleic acid molecule of claim 51 which is cDNA. *Serial No. 10/084,700: page 17, lines 4-12* *Serial No. 60/070,182: page 14, par. 1*	**23.** The DNA molecule of claim 22, which is a cDNA comprising a sequence approximately 1.3 kilobase pairs in length that encodes said human BUB3 protein.
53. (new) An isolated RNA molecule transcribed from the nucleic acid molecule of claim 50. *Serial No. 10/084,700: Example 2* *Serial No. 60/070,182: Example 1*	**25.** An isolated RNA molecule transcribed from the nucleic acid of claim 21.
54. (new) An antibody immunologically specific for the isolated protein of claim 42. *Serial No. 10/084,700: page 12, lines 11-1* *Serial No. 60/070,182: page 16, lines 6-13*	**29.** An antibody immunologically specific for the isolated protein of claim 28.

Showing Under 37 C.F.R. § 41.202(d)

U.S. Patent 6,593,098 (Yen) claims a priority date of December 1, 1997. Before December 1, 1997, Applicant conceived of and reduced to practice the subject matter of each of pending claims 4 and 42 and new claims 49-54.[2]

The evidence set forth below documents activities of inventor Todd W. Seeley and two scientists who worked under his direction. All of these activities took place before Yen's claimed priority date of December 1, 1997. The evidence includes:

- testimony and notebook records of Dr. Seeley;
- corroborating testimony of Dr. Seeley's colleague Dr. David Duhl, who witnessed Dr. Seeley's notebook records;
- corroborating testimony and notebook records of Dr. Seeley's laboratory technician, Ms. Ling Wang; and
- corroborating testimony and notebook records of Ms. Chun Ting Lee-Ng, who worked in Chiron's sequencing facility.

This evidence demonstrates that Dr. Seeley conceived of and reduced to practice the subject matter of each of claims 4, 42, and 49-54 before December 1, 1997. Specifically, before December 1, 1997, Dr. Seeley conceived of and actually reduced to practice a nucleic acid molecule that encodes huBUB3 protein, huBUB3 protein itself, huBUB3 mRNA, a huBUB3 fusion protein, and huBUB3 antibodies. Before December 1, 1997, Dr. Seeley recognized and demonstrated utilities for each of these molecules. Based on the evidence, even if Yen were

[2] Applicant reserves the right to show diligence in carrying out his inventive activity, including that described herein, at an appropriate time and to otherwise supplement this evidence if necessary in an interference.

entitled to a December 1, 1997 constructive reduction to practice, Applicant is entitled to priority of invention under 35 U.S.C. § 102(g).[3]

1. Before December 1, 1997, Dr. Seeley conceived of the huBUB3 open reading frame and the encoded huBUB3 protein.[4]

Before Dr. Seeley began his work with huBUB3, he knew that the yeast proteins BUB3 and BUB1 were involved in the normal control of mitosis in yeast. SD ¶ 4. He knew that a complex of both proteins is required for cell cycle arrest to occur in response to disruption of the spindle by microtubule poisons. SD ¶ 4; SD Ex. 21; SD Ex. 22. Dr. Seeley was interested in identifying human proteins that carry out similar functions because he knew that microtubule poisons, such as vinblastine, vincristine, and taxol, are commonly used cancer chemotherapeutic agents. SD ¶ 4. He thought that proteins that would interfere with cell cycle arrest in cancer cells treated with microtubule poisons would be useful therapeutic targets; he reasoned that, if cell cycle arrest did not occur, the effect of the microtubule poison could be potentiated. SD ¶ 4.

Dr. Seeley obtained the human homolog of BUB1, huBUB1, which is described in Dr. Seeley's patent 6,489,137. SD ¶ 5; SD Ex. 23. To obtain a human homolog of BUB3, Dr. Seeley "reverse translated" the *S. cerevisiae* (yeast) BUB3 protein sequence to obtain nucleotide sequences that could encode the yeast protein and used those sequences to conduct searches of public databases. SD ¶ 6; SD Ex. 1, page 1. Dr. Seeley identified from these searches a mouse

[3] Applicant does not concede that Yen is entitled to a constructive reduction to practice as of December 1, 1997 for the inventions embraced by the pending claims. Applicant reserves the right to challenge Yen's priority claim at an appropriate time.

[4] As demonstrated by the cited evidence, all of the events discussed in this and the following sections took place prior to December 1, 1997. Applicant provides this footnote so as not to burden the discussion with repeated statements that all of these events took place before December 1, 1997.

cDNA clone, aligned the predicted amino acid sequence encoded by the mouse cDNA clone with the amino acid sequence of yeast scBUB3, and identified the mouse cDNA clone as a potential murine homolog of the yeast gene scBUB3. SD ¶ 6; SD Ex. 1, page 1; SD Ex. 2.

Using the mouse nucleotide sequence and the nucleotide sequences he obtained by reverse translating the yeast BUB3 protein sequence, Dr. Seeley next identified human ESTs that spanned the mouse cDNA sequence. SD ¶ 7. He compiled the human ESTs into a single sequence, which he identified as a coding sequence for a human BUB3 homolog, huBUB3. SD ¶ 7; SD Ex. 1, page 2.

Dr. Seeley documented his conception of the huBUB3 coding sequence in an invention disclosure. SD ¶ 8, SD Ex. 2. Dr. Seeley's invention disclosure also contains his conception of the amino acid sequence of the huBUB3 protein and describes various utilities for huBUB3. SD ¶ 8; SD Ex. 2. Dr. Seeley sent the invention disclosure to Chiron's Intellectual Property Department. SD ¶ 9; SD Ex. 2.[5]

2. Before December 1, 1997, Dr. Seeley actually reduced to practice a huBUB3 nucleic acid molecule.

Dr. Seeley then cloned a huBUB3 cDNA from a human testis cDNA library and ligated the huBUB3 cDNA clone into a plasmid vector. SD ¶¶ 10-13. Dr. Seeley gave preparations of the plasmids he obtained to his laboratory technician, Ms. Ling Wang, so that she could purify the plasmid DNA and verify the size and orientation of the cDNA inserts. SD ¶ 13; Wang Declaration (WD) ¶ 4; WD Ex. 1.

[5] The nucleotide sequence in Dr. Seeley's invention disclosure is identical to that in provisional application Serial No. 60/070,184 and in pending application Serial No. 10/084,700 but for one nucleotide. See page 11, below, and Appendix 1. The one nucleotide difference does not affect the amino acid sequence of the encoded huBUB3 protein. See Appendix 2.

Ms. Wang's testimony corroborates Dr. Seeley's conception and reduction to practice of the huBUB3 clone. Ms. Wang knew that Dr. Seeley had made the plasmids he gave her and knew the plasmids should contain a huBUB3 cDNA insert of a particular size. WD ¶ 4; WD Ex. 1, pages 1 and 2. Ms. Wang determined that a plasmid identified as "291-2" contained a huBUB3 cDNA insert of the correct size and in the correct (sense) orientation. WD ¶¶ 5-7; WD Ex. 1. Ms. Wang also remembers ordering and/or preparing the reagents for her huBUB3 work (WD ¶ 8), attending lab meetings with Dr. Seeley at which huBUB3 was discussed (WD ¶ 9), and regularly discussing experimental results with Dr. Seeley (WD ¶ 10).

After confirming the size and orientation of the huBUB3 cDNA insert, Ms. Wang recorded in her notebook her plan to make a large scale preparation of clone 291-2 and send it to Chiron's DNA sequencing service for sequencing. WD ¶ 7; SD ¶ 14.

The testimony of Ms. Chun Ting Lee-Ng, who worked in Chiron's sequencing facility, also corroborates Dr. Seeley's conception of the huBUB3 nucleotide and amino acid sequences and his reduction to practice of the huBUB3 cDNA. Ms. Lee-Ng received a Request Form from Dr. Seeley asking her to sequence a particular clone. Lee-Ng Declaration (L-ND) ¶ 6; L-ND Ex. 1, page 1. The request form identified the clone as "291-2" and indicated that Dr. Seeley provided Ms. Lee-Ng with its "proposed" sequence. L-ND ¶ 6; L-ND Ex. 1, pages 1 and 2.

Ms. Lee-Ng documented in her laboratory notebook the primers she selected to amplify the huBUB3 cDNA and the dilution and amount of the DNA preparation she used to sequence clone 291-2. L-ND ¶ 7; L-ND Ex. 1, page 3. After Ms. Lee-Ng finished sequencing the 291-2 clone, she aligned its sequence with the proposed sequence that Dr. Seeley had given her. L-ND ¶ 9; L-ND Ex. 1, page 5. Ms. Lee-Ng attached a copy of the sequence alignment and the completed sequencing Request Form in her notebook. L-ND ¶ 9; L-ND Ex. 1, page 5.

According to her typical practice, Ms. Lee-Ng sent the completed request form and the sequencing results to Dr. Seeley promptly after she completed the sequencing. L-ND ¶ 8. Dr. Seeley's notebook contains a copy of Ms. Lee-Ng's sequence alignment, which confirms he received the sequencing results. SD ¶ 19; SD Ex. 10. Dr. Seeley noted that the sequence of the huBUB3 cDNA in clone 291-2 matched his predicted sequence except at one position where, based on the human ESTs he used to assemble the sequence, he had selected adenine (A) instead of cytosine (C). SD ¶ 19; SD Ex. 10. Because of the redundancy of the genetic code, this single nucleotide difference does not affect the amino acid sequence encoded by the huBUB3 cDNA. See Appendix 2. Nucleotides 60-1126 of SEQ ID NO:1 of the present application are identical to the nucleotide sequence Ms. Lee-Ng confirmed for Dr. Seeley. See Appendix 1.

3. Before December 1, 1997, Dr. Seeley actually reduced huBUB3 mRNA to practice and demonstrated its differential expression.

Dr. Seeley prepared a radiolabeled probe derived from a huBUB3 cDNA clone and used it to probe a commercial Northern blot containing mRNA isolated from a variety of human organs. SD ¶ 17; SD Ex. 8. Ms. Wang remembers seeing these Northern blots. WD ¶ 10.

Dr. Seeley determined from the Northern blots that huBUB3 mRNA is expressed at low levels in many tissues and is significantly over-expressed in adult testis, which is a tissue with a high level of cell proliferation. SD ¶ 17. These results suggested to Dr. Seeley that huBUB3 performs a common function in cell proliferation that is shared by cells in various tissues. SD ¶ 17.

4. Before December 1, 1997, Dr. Seeley actually reduced to practice huBUB3 protein and a huBUB3 fusion protein.

Dr. Seeley already had prepared a construct (291-2) from which to express huBUB3 protein. SD ¶¶ 10-14, 19; SD Ex. 10; WD ¶¶ 4-7; WD Ex. 1; L-ND ¶ 6; L-ND Ex. 1. Dr. Seeley also prepared an expression construct that could express a fusion protein containing huBUB3 protein fused to a synthetic FLAG immuno-peptide ("huBUB3-FLAG") and made a large-scale preparation of the expression construct. SD ¶¶ 22-25; SD Ex. 14.

Dr. Seeley used the huBUB3-FLAG expression construct and huBUB3 clone 291-2 to express ^{35}S-labeled huBUB3 and huBUB3-FLAG proteins using an *in vitro* transcription/translation kit. SD ¶ 26; SD Ex. 15. He separated the ^{35}S-labeled expressed proteins using SDS-polyacrylamide gel electrophoresis, visualized the proteins using X-ray film, and demonstrated that the proteins had the molecular weights he expected. SD ¶¶ 26-27; SD Ex. 16.

5. Before December 1, 1997, Dr. Seeley demonstrated that huBUB3 binds to huBUB1.

Yeast BUB3 protein binds to yeast BUB1 protein. SD ¶¶ 4, 30; SD Ex. 21; SD Ex 22. Dr. Seeley demonstrated that the huBUB3 protein binds to the human homolog of BUB1 (huBUB1). SD ¶ 31. First, Dr. Seeley repeated the *in vitro* transcription/translation reaction and used the proteins it produced to demonstrate that an anti-FLAG monoclonal antibody could immunoprecipitate the FLAG-huBUB3 fusion protein. SD ¶¶ 28-30; SD Ex. 17.

Dr. Seeley next carried out another *in vitro* transcription/translation reaction with a mixture of plasmids, including plasmids encoding huBUB3, FLAG-huBUB3, and huBUB1. SD ¶ 31; SD Ex. 18. Dr. Seeley immunoprecipitated the ^{35}S-labeled translation products using the anti-FLAG monoclonal antibody. SD ¶ 31; SD Ex. 18. He separated the proteins on an SDS-

polyacrylamide gel, dried the gel, and exposed it to X-ray film to visualize the ^{35}S-labeled proteins. SD ¶ 32; Ex. 18. Dr. Seeley concluded from this experiment that FLAG immunoprecipitation could be used to observe association between BUB1 and FLAG-BUB3. SD ¶ 33.

Dr. Seeley then repeated the co-immunoprecipitation experiment with FLAG-huBUB3 and huBUB1. SD ¶ 34; SD Ex. 19. He demonstrated with this experiment that huBUB1 co-precipitated with FLAG-huBUB3, which indicated to him that huBUB3 is a ligand for huBUB1. SD ¶ 35; SD Ex. 17.

Dr. Seeley recognized that the results of his experiments were consistent with a model in which huBUB3/huBUB1 complexes retain a single monomer of huBUB3 per complex and the labeled FLAG-huBUB3 protein competes with huBUB3 for a single binding site in the complex such that prior binding of labeled FLAG-huBUB3 precludes association with huBUB3 protein. SD ¶ 35. Dr. Seeley also recognized that his results were consistent with a model in which huBUB3 does not self-associate. SD ¶ 35.

When Dr. Seeley knew that huBUB3 bound to huBUB1, it confirmed his belief that these proteins (huBUB1, huBUB3, and FLAG-huBUB3) were useful for identifying agents for disrupting huBUB3-huBUB1 binding and, therefore, for potentiating the effect of microtubule poisons used to treat cancer, *i.e.*, cancer chemotherapy, and the development of new therapeutics. SD ¶¶ 8, 36.

6. Before December 1, 1997 Dr. Seeley prepared huBUB3 antibodies

Dr. Seeley produced antibodies to huBUB3 protein by direct DNA immunization of mice with a huBUB3 expression construct (plasmid 291-2). SD ¶ 37. Dr. Seeley referred to these antibodies in a list of results he presented at a meeting with his supervisor, Lewis T. ("Rusty") Williams. SD ¶ 37; SD Ex. 20.

The testimony and documents summarized above and provided with this paper establish by a preponderance of evidence that Dr. Seeley conceived of and actually reduced to practice a nucleic acid molecule that encodes huBUB3 protein, huBUB3 protein itself, huBUB3 mRNA, a huBUB3 fusion protein, and huBUB3 antibodies. The evidence establishes that, before December 1, 1997, Dr. Seeley recognized and demonstrated utilities for each of these molecules. Based on this evidence, even if Yen were entitled to a constructive reduction to practice as of December 1, 1997, Applicant is entitled to priority of invention under 35 U.S.C. § 102(g).

Respectfully submitted,
BANNER & WITCOFF, LTD.

Date: April 1, 2005

By: Lisa M. Hemmendinger
Joseph M. Skerpon
Registration No. 29,864

Lisa M. Hemmendinger
Registration No. 42,653

Customer No. 22907